PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

12/5

PCT

To:
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Global Intellectual Property
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	25 -02- 2005
Applicant's or agent's file reference 101270-1 WO	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE04/01589	03/11/2004	03/11/2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/437, A61P1/04

Applicant
ASTRAZENECA AB et al

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further opinions, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language, _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims		YES
	Claims	4-11, 15-19	NO
Inventive step (IS)	Claims		YES
	Claims	4-11, 15-19	NO
Industrial applicability (IA)	Claims	4-11, 15-19	YES
	Claims		NO

2. Citations and explanations:

The object of the invention is the use of P-CABs for the production of medicaments for the treatment of sleep disturbance due to silent gastro-esophageal reflux. Another object of the invention is the use of reversible proton pump inhibitors for the production of medicaments for the treatment of sleep disturbance due to silent gastro-esophageal reflux.

Reference is made to the following document/documents:

D1: WO9955706

D2: Kaminsky, J.J. et al., "Antiulcer agents. 4. Conformational Considerations and the Antiulcer Activity of Substituted Imidazo[1,2-a]pyridines and Related Analogues", J. Med. Chem. 1989, 32, 1686-1700.

D3: WO0017200

D4: Vakil, N., "Review article: new pharmacological agents for the treatment of gastro-esophageal reflux disease," Aliment Pharmocol. Ther. 2004, 19, 1041-1049.

D5: Sachs, G. et al., "Current trends in the treatment of upper gastrointestinal disease," Best Pract. Res. Clin. Gastroenterol. 2002, 16, 835-849.

D6: Wurst, W. and Hartmann, M., "Current Status of Acid Pump Antagonists (Reversible PPIs)," Yale J. Biol. Med. 1996, 69, 233-243.

D7: Pope, A. and Sachs, G., "Reversible inhibitors of the gastric (H+/K+)-ATPase as both potentional therapeutic agents and probes of pump function," Biochem. Soc. Trans. 1992, 20, 566-572.

D8: Wallmark, B. et al., "Inhibition of Gastric H+,K+-ATPase

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

and Acid Secretion by SCH28080, a Substituted Pyridyl(1,2a)imidazole," J. Biol. Chem. 1987, 262, 2077-2084.

Document D1 discloses compounds of the formula I with substituents R1-R7 and X as defined in claim 1 (p 56-57). These compounds can be used for prevention and treatment of gastric-acid related diseases including reflux esophagitis (p 15).

Consequently, the subject matter of claims 4-11, 15-18 is previously known and therefore, these claims are not approved.

Document D2 is regarded as being the closest prior art to the subject-matter of claims 4-11, 15-18 and discloses substituted imidazo[1,2-a]pyridines that are highly similar to the compounds in the present invention (see especially compound 8, table I), and discloses their gastric antisecretory activity and their competitive and reversible interaction with the high-affinity potassium ion (K+) binding site of the gastric proton pump enzyme H+/K+-ATPase.

The subject-matter of claims 4-11, 15-18 therefore differs from this known document D2 in that compounds with an additional amino-substituent on the pyridine-ring are used.

Consequently, with the background of D2, the problem is to develop differently substituted imidazo[1,2-a]pyridine derivatives for use of prevention and treatment of gastric-acid related diseases.

The solution proposed in claims 4-11, 15-18 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

Claims 4-11, 15-18 relate to a selection of compounds from a range of compounds according to the general structure of substituted imidazo[1,2-a]pyridine. Such a selection can only be regarded as inventive, if the choice of the novel compounds in the present patent application presents unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claims 4-11, 15-18.

Document D3 discloses the use of soraprazan for the prevention and treatment of gastro-intestinal inflammatory diseases, which can be caused by gastric acid.

Consequently, the subject matter of claim 19 is previously known and therefore, this claim is not approved.

Document D4-D8 are literature articles reporting on potassium-competitive inhibitors of the enzyme H+/K+-ATPase and their use for the treatment of gastro-esophageal reflux disease.

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Box No. VII Certain defects in the international application

The following defects in the form or content of the international application have been noted:

According to the requirements of Rule 10.2 PCT, the terminology and the signs shall be consistent throughout the application. This requirement is not met in view of the use of the expressions potassium-competitive acid blocker (P-CAB) and reversible proton pump inhibitor for the same feature, namely substituted imidazo[1,2-a]pyridines that exhibit gastric antisecretory activity and competitive and reversible interaction with the high-affinity potassium ion (K+) binding site of the gastric proton pump enzyme H+/K+-ATPase.